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Certifying Officer

Box Provisional Application
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. § 1.53 (c).

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TITLE OF THE INVENTION (280 characters max)

NOVEL BENZIMIDAZOLE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS COMPRISING THESE COMPOUNDS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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☐ Application Data Sheet. See 37 CFR 1.76.
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☒ A check or money order is enclosed to cover the Provisional filing fees.	☒ Large Entity ($160.00)
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

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NOVEL BENZIMIDAZOLE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS COMPRISING THESE COMPOUNDS

TECHNICAL FIELD

The present invention relates to novel benzimidazole derivatives, pharmaceutical compositions containing these compounds, and methods of treatment therewith.

The compounds of the invention are useful in the treatment of central nervous system diseases and disorders, which are responsive to modulation of the $GABA_A$ receptor complex, and in particular for inducing and maintaining anaesthesia, sedation and muscle relaxation, as well as for combating febrile convulsions in children.

The compounds of the invention may also be used by veterinarians.

BACKGROUND ART

Agents that bind or interact with the modulatory sites on the $GABA_A$ receptor complex, such as for example the benzodiazepine receptor, can have either enhancing effect on the action of GABA, i.e. a positive modulatory effect of the receptor (agonists, partial agonists), an attenuating effect on the action of GABA, i.e. negative modulation of the receptor (inverse agonists, partial inverse agonists), or they can block the effect of both agonists and inverse agonists (antagonists or ligands without intrinsic activity).

Agonists generally produce muscle relaxant, hypnotic, sedative, anxiolytic, and/or anticonvulsant effects, while inverse agonists produce pro-convulsive, anti-inebriant or anxiogenic effects. Compounds with anxiolytic effects, but with or without reduced muscle relaxant, hypnotic and sedative effects, are characterised as partial agonists. Partial inverse agonists are considered to be useful as cognition enhancers.

Full agonists of the benzodiazepine receptor are considered useful as anaesthetics. However, many drugs presently available as anaesthetics, and especially pre-anaesthetics, give rise to hang-over effects as well as long awakening times, wherein careful monitoring of the patient is necessary. Anaesthetics with a long half-life may also impose difficulties during incidents of overdosing i.e. prolonged respiratory depression. Furthermore, some currently used drugs cannot be used for anaesthetising children as deaths have been reported in children after prolonged use of Propofol. Some anaesthetics are gasses, which inherently possesses a contamination problem for the medical staff.

A well known anaesthetic, Propofol, is administered as a mixture of soybean oil, glycerol and purified egg phosphatide, which mixture nourish bacterial growth.

Administration of bacterially contaminated Propofol has been reported to cause sepsis and death [*Wiklund et al.*; The New England Journal of Medicine 1997 **337** (16) 1132-1141]. Further, compounds with a long *in vivo* half-life will give problems with accumulation during and after prolonged treatment e.g. when administered to patients constrained to a respirator. Short half-lives wherein the compounds are metabolised to inactive metabolites allow for a predictable correlation of dose and duration of pharmacological effect.

Ideally the anaesthestising effect should be observed shortly after a bolus injection or infusion of the compound. A rapid onset of action minimises the period of anxiety and uneasiness experienced by patients going into surgery.

Patients suffering from severe and continuous epileptic attacks presently treated with large amounts of sedatives, e.g. benzodiazepines, will benefit from shorter acting compounds with no hang-over or long lasting sedating effect.

As the preferred route of administration is by intravenous injection or infusion, the anaesthestising compounds should preferably be water soluble.

EP 616807 describes benzimidazole compounds for use as benzodiazepine receptor ligands.

WO 96/33194, WO 96/33191 and WO 96/33192 describe benzimidazole compounds having affinity for the GABA receptor complex.

WO 98/34923 describes phenylbenzimidazole derivatives as ligands for the GABA receptor complex.

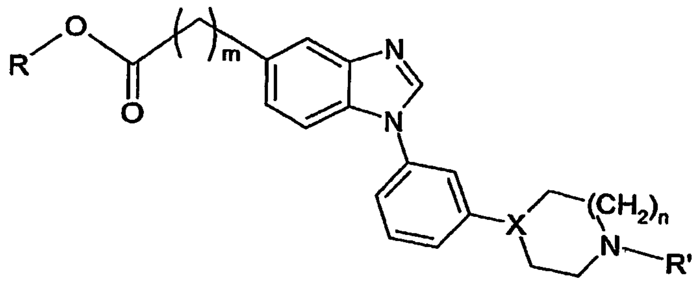
WO 98/17651, WO 00/78728 and WO 02/050057 describe benzimidazole compounds for use as e.g. anaesthetics.

However, there is a continued strong need to find compounds with an optimized pharmacological profile.

SUMMARY OF THE INVENTION

It is an object of the invention to provide novel compounds useful as anaesthetics and/or pre-anaesthetics, sedatives, muscle relaxants, and for the treatment of febrile convulsions in children, status epilepticus, for use to patients constrained to a respirator as well as for veterinarian uses. A further object of the invention is to produce compounds which show a rapid onset of action. A still further object of the invention is to produce compounds with less hang-over effect and/or less long lasting sedation effect thereby showing a faster recovery of the patients.

In its first aspect, the invention provides a compound of general formula I:



(I)

or a pharmaceutically acceptable salt thereof, or an N-oxide thereof, wherein R, R', X, m and n are defined as below.

In its second aspect, the invention provides a pharmaceutical composition containing a therapeutically effective amount of a compound according to the invention, or an N-oxide thereof, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In its third aspect, the invention provides a use of a compound according to the invention, or an N-oxide thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of the GABA receptor complex.

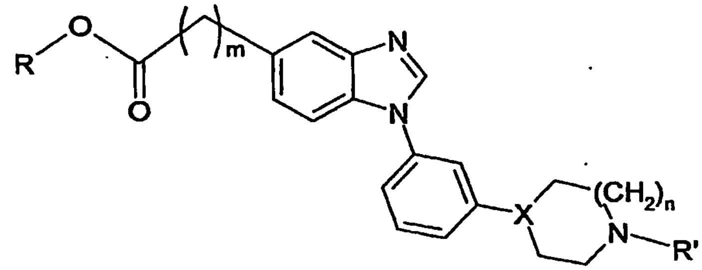
In its fourth aspect, the invention provides a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of the GABA receptor complex, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to the invention, or an N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and the working examples.

DETAILED DISCLOSURE OF THE INVENTION

Benzimidazole Derivatives

In its first aspect the invention provides novel compounds. The compounds of the invention are represented by general formula I:



(I)

or an N-oxide thereof, or a pharmaceutically acceptable salt thereof, wherein
R represents alkyl, hydroxyalkyl, alkoxyalkyl, R^aR^bN-alkyl, R^aR^bN-CO-alkyl, or phenyl-alkyl;

wherein R^a and R^b independently of each other represents hydrogen or alkyl;

R' represents alkoxyalkyl, alkoxyalkenyl, alkoxyalkynyl, alkylcarbonylalkyl, alkenyl, or alkynyl;

m is 0 or 1;

n is 1 or 2;

X represents N or CH.

In one embodiment of the compound general formula I, n is 1 and X represents N.

In a second embodiment of the compound of general formula I, n is 1 and X represents CH.

In a further embodiment of the compound of general formula I, R represents alkyl, hydroxyalkyl, or alkoxyalkyl. In a special embodiment, R represents alkyl, such as methyl, ethyl, n-butyl, or iso-butyl. In a further embodiment, R represents hydroalkyl, such as hydroxymethyl or hydroxyethyl. In a still further embodiment, R represents alkoxyalkyl. In a special embodiment, R represents alkoxyethyl, such as methoxyethyl.

In a further embodiment of the compound of general formula I, R represents R^aR^bN-alkyl, R^aR^bN-CO-alkyl, or phenyl-alkyl. In a further embodiment, R represents R^aR^bN-alkyl or R^aR^bN-CO-alkyl, wherein R^a and R^b independently of each other represents hydrogen, methyl or ethyl. In a special embodiment, R represents R^aR^bN-alkyl. In a further embodiment, R represents methylaminoalkyl or dimethylaminoalkyl, such as methylaminoethyl or dimethylaminoethyl. In a still further embodiment, R represents R^aR^bN-CO-alkyl. In a further embodiment, R represents methylcarbamoylalkyl, ethylcarbamoylalkyl, or dimethylcarbamoylalkyl, such as methylcarbamoylmethyl, ethylcarbamoylmethyl or dimethylcarbamoylmethyl. In a still further embodiment, R represents phenyl-alkyl, such as phenylmethyl.

In a further embodiment of the compound of general formula I, R^a and R^b independently of each other represents hydrogen, methyl or ethyl. In one

embodiment, R^a represents hydrogen. In a second embodiment, R^a represents methyl. In a further embodiment, R^a represents ethyl. In a still further embodiment, R^b represents hydrogen. In a further embodiment, R^b represents methyl. In a still further embodiment, R^b represents ethyl. In a further embodiment, R^a represents methyl and R^b represents methyl. In a still further embodiment, R^a represents methyl and R^b represents hydrogen. In a further embodiment, R^a represents ethyl and R^b represents hydrogen.

In a further embodiment of the compound of general formula I, R' represents alkoxyalkyl. In a special embodiment, R' represents alkoxyethyl, such as methoxyethyl or ethoxyethyl. In a further embodiment, R' represents methoxyalkyl. In a still further embodiment, R' represents ethoxyalkyl.

In a further embodiment of the compound of general formula I, R' represents alkylcarbonylalkyl, alkenyl, or alkynyl. In one embodiment, R' represents alkylcarbonylalkyl, such as methylcarbonylalkyl or alkylcarbonylmethyl. In a special embodiment, R' represents methylcarbonylmethyl. In a further embodiment, R' represents alkenyl, such as propenyl. In a special embodiment, R' represents allyl. In a still further embodiment, R' represents alkynyl, such as propynyl. In a special embodiment, R' represents propargyl.

In a still further embodiment of the compound of general formula I, R represents alkyl, R' represents alkoxyalkyl, m is 0, n is 1 and X represents N.

In a further embodiment of the compound of general formula I, R represents hydroxyalkyl, R' represents alkoxyalkyl, m is 0, n is 1 and X represents N.

In a still further embodiment of the compound of general formula I, R represents alkoxyalkyl, R' represents alkoxyalkyl, m is 0, n is 1 and X represents N.

In a still further embodiment of the compound of general formula I, R represents alkyl, R' represents alkoxyalkyl, m is 1, n is 1 and X represents N.

In a further embodiment of the compound of general formula I, R represents hydroxyalkyl, R' represents alkoxyalkyl, m is 1, n is 1 and X represents N.

In a still further embodiment of the compound of general formula I, R represents alkyl, R' represents alkoxyalkyl, m is 0, n is 1 and X represents CH.

In a further embodiment of the compound of general formula I, R represents hydroxyalkyl, R' represents alkynyl, m is 0, n is 1 and X represents N.

In a still further embodiment of the compound of general formula I, R represents alkoxyalkyl, R' represents alkenyl, m is 0, n is 1 and X represents N.

In a further embodiment of the compound of general formula I, R represents alkoxyalkyl, R' represents alkynyl, m is 0, n is 1 and X represents N.

In a still further embodiment of the compound of general formula I, R represents alkoxyalkyl, R' represents alkylcarbonylalkyl, m is 0, n is 1 and X represents N.

In a further embodiment of the compound of general formula I, R represents phenylalkyl, R' represents alkoxyalkyl, m is 0, n is 1 and X represents N.

In a still further embodiment of the compound of general formula I, R represents R^aR^bN-alkyl, R' represents alkoxyalkyl, m is 0, n is 1 and X represents N.

In a still further embodiment of the compound of general formula I, R represents R^aR^bN-CO-alkyl, R' represents alkoxyalkyl, m is 0, n is 1 and X represents N.

In a special embodiment the chemical compound of the invention is
2-Methoxyethyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1a**);
2-Hydroxyethyl 1-(3-(4-ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1b**);
n-Butyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1c**);
iso-Butyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1d**);
2-Methoxyethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1e**);
2-Hydroxyethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1f**);
n-Butyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1g**);
iso-Butyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1h**);
5-(methoxycarbonylmethyl) 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole (**1i**);
5-(2-hydroxyethoxycarbonylmethyl) 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole (**1j**);
2-Methoxyethyl 1-(3-(4-(propargyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**8a**);
2-Methoxyethyl 1-(3-(4-(allyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**8b**);
2-Methoxyethyl 1-(3-(4-(2-oxo-propyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**8c**);
2-Methoxyethyl 1-(3-(1-methoxyethyl-4-piperidinyl)-phenyl)-benzimidazole-5-carboxylate (**8d**);
2-Hydroxyethyl 1-(3-(4-(propargyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**8e**);
Benzyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10a**);

Methylcarbamoylmethyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10b**);
Ethylcarbamoylmethyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10c**);
2-Dimethylaminoethyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10d**);
Benzyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10e**);
Methylcarbamoylmethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10f**);
Ethylcarbamoylmethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10g**);
2-Dimethylaminoethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10h**);
or an N-oxide thereof, or a pharmaceutically acceptable salt thereof.

Definition of Substituents

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to six carbon atoms (C_{1-6}-alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention an alkenyl group designates a carbon chain containing one or more double bonds, including di-enes, tri-enes and poly-enes. In a preferred embodiment the alkenyl group of the invention comprises of from two to six carbon atoms (C_{2-6}-alkenyl), including at least one double bond. In a most preferred embodiment the alkenyl group of the invention is ethenyl; 1- or 2-propenyl; 1-, 2- or 3-butenyl, or 1,3-butdienyl; 1-, 2-, 3-, 4- or 5-hexenyl, or 1,3-hexdienyl, or 1,3,5-hextrienyl.

In the context of this invention an alkynyl group designates a carbon chain containing one or more triple bonds, including di-ynes, tri-ynes and poly-ynes. In a preferred embodiment the alkynyl group of the invention comprises of from two to six carbon atoms (C_{2-6}-alkynyl), including at least one triple bond. In its most preferred embodiment the alkynyl group of the invention is ethynyl; 1-, or 2-propynyl; 1-, 2-, or 3-butynyl, or 1,3-butdiynyl; 1-, 2-, 3-, 4-pentynyl, or 1,3-pentdiynyl; 1-, 2-, 3-, 4-, or 5-henynyl, or 1,3-hexdiynyl or 1,3,5-hextriynyl.

Alkoxy means O-alkyl, wherein alkyl is as defined above.

Alkoxyalkyl means alkoxy as above and alkyl as above, meaning for example, methoxymethyl.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Metal salts of a chemical compound of the invention include alkali metal salts such as the sodium salt of a chemical compound of the invention containing a carboxy group.

Examples of pre- or prodrug forms of the chemical compound of the invention include examples of suitable prodrugs of the substances according to the invention include compounds modified at one or more reactive or derivatizable groups of the parent compound. Of particular interest are compounds modified at a carboxyl group, a hydroxyl group, or an amino group. Examples of suitable derivatives are esters or amides.

The chemical compound of the invention may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvent such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

Steric Isomers

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms (±). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Moreover, some of the chemical compounds of the invention having an alkenyl group, may exist in two forms, syn- and anti-form (Z- and E-form), depending on the arrangement of the substituents around the -C=C- double bond. A chemical compound of the present invention may thus be the syn- or the anti-form (Z- and E-form), or it may be a mixture hereof.

N-oxides

In the context of this invention an N-oxide designates an oxide derivative of a nitrogen containing compound, e.g. N-containing heterocyclic compounds capable of forming such N-oxides, and compounds holding one or more amino groups. For example, the N-oxide of a compound containing a pyridyl may be the 1-oxy-pyridin-2, -3 or -4-yl derivative.

N-oxides of the compounds of the invention may be prepared by oxidation of the corresponding nitrogen base using a conventional oxidizing agent such as hydrogen peroxide in the presence of an acid such as acetic acid at an elevated temperature, or by reaction with a peracid such as peracetic acid in a suitable solvent, e.g. dichloromethane, ethyl acetate or methyl acetate, or in chloroform or dichloromethane with 3-chloroperoxybenzoic acid.

Labelled Compounds

The compounds of the invention may be used in their labelled or unlabelled form. In the context of this invention "label" stands for the binding of a marker to the compound of interest that will allow easy quantitative detection of said compound.

The labelled compounds of the invention may be useful as diagnostic tools, radio tracers, or monitoring agents in various diagnostic methods, and for *in vivo* receptor imaging.

The labelled isomer of the invention preferably contains at least one radionuclide as a label. Positron emitting radionuclides are all candidates for usage. In the context of this invention the radionuclide is preferably selected from ^{2}H (deuterium), ^{3}H (tritium), ^{13}C, ^{14}C, ^{131}I, ^{125}I, ^{123}I, and ^{18}F.

The physical method for detecting the labelled isomer of the present invention may be selected from Position Emission Tomography (PET), Single Photon Imaging Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT), or combinations thereof.

Methods of Preparation

The chemical compounds of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

The compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention.

While a compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a

pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising a compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suit the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

Biological Activity

The compounds of the invention are particularly useful as anaesthetics and/or pre-anaesthetics, for inducing and maintaining anaesthesia, as sedatives, as muscle

relaxants, and for combating febrile convulsions in children, status epilepticus, for use to patients constrained to a respirator.

The compounds of the invention show a short duration of action, they are water soluble at therapeutic relevant doses, and are particular well suited for intravenous administration.

The compounds of the invention may also be used by veterinarians.

The compounds of the invention show high to moderate affinity for the benzodiazepine receptor as measured by displacement at ^{3}H-flunitrazepam *in vitro* as well as *in vivo*. The most preferred compounds are full agonists i.e. they exert a high maximal effect in the seizure test as described in the application.

Preferred compounds are full agonists on the $GABA_A$ receptor complex, e.g. as measured by the anticonvulsant activity in the ptz-test as described in Test method 2. The compounds of the invention show half-lives of below 30 minutes, which allows for a short duration of action. Preferred half-lives are in the range of from about 30 seconds to about 20 minutes. Most preferred half-lives are in the range of from about 2 to about 5 minutes.

The preferred compounds induce a rapid onset of anaesthesia, i.e. in less than 1-2 minutes. Most preferred is an onset of anaesthesia in less than 1 minute.

Awakening from anaesthesia following a bolus injection (i.v.), or following the attenuation of an infusion, should occur within a short period of time, i.e. of from about 5 to about 30 minutes, preferably of from about 5 to about 10 minutes, after which time the patient should normalise rapidly, i.e. in less than 40 minutes, preferably in less than 20 minutes, as measured from awakening.

The compounds of this invention can be used together with analgetic compounds such as Remifentanile, Fentanyl, or other opiods.

Methods of Therapy

In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to modulation of the GABA receptor complex, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of compound according to the invention, or an N-oxide thereof, or a pharmaceutically acceptable salt thereof.

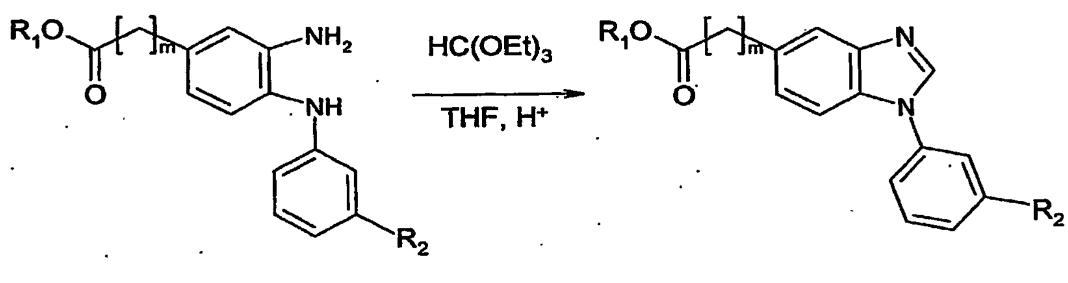
In a more preferred embodiment the invention provides a method for the induction or maintenance of anaesthesia or pre-anaesthesia, muscle relaxation or sedation, or for the treatment, prevention or alleviation of fewer cramps or status epilepticus.

It is at present contemplated that suitable infusion rates are in the range of from about 0.01 to about 100 mg/kg/hour, more preferred of from about 0.1 to about 15 mg/kg/hour, dependent upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

Example 1
Method A:



2a-i **1a-i**

The benzimidazoles of Table 1 were all prepared according to the above scheme.

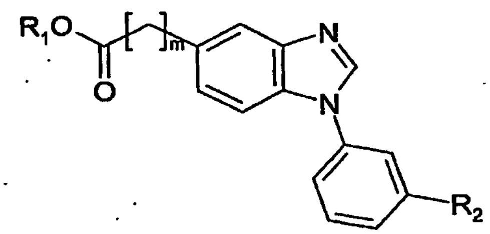
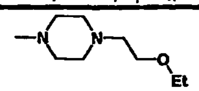
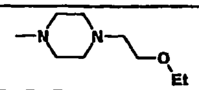
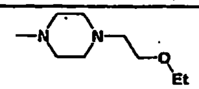
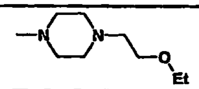
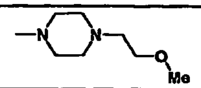
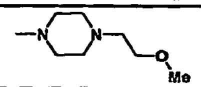
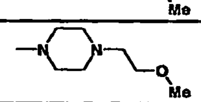
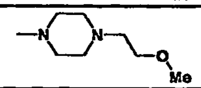
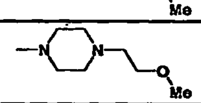
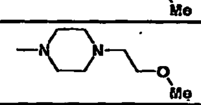


Table 1

Comp. No.	R_1	R_2	m	Mp (°C)	Yield (%)	Starting material	Salt
1a	$MeO(CH_2)_2$		0	A	52	**2a**	HCl
1b	$HO(CH_2)_2$		0	A	47	**2b**	HCl
1c	$Me(CH_2)_3$		0	92-95	54	**2c**	HCl
1d	$(CH_3)_2CHCH_2$		0	154-160	58	**2d**	HCl
1e	$MeO(CH_2)_2$		0	173-178	45	**2e**	HCl
1f	$HO(CH_2)_2$		0	159-162	38	**2f**	HCl
1g	$Me(CH_2)_3$		0	148-152	59	**2g**	HCl
1h	$(CH_3)_2CHCH_2$		0	159-163	25	**2h**	HCl
1i	Me		1	A	60	**2i**	-
1j	$HO(CH_2)_2$		1	A	88	**1i**	HCl

The yield is given for a total of 3 steps starting from **4a-b** and **5a-e**. A few these compounds were hygroscopic solids, therefore no melting points were recorded. Instead these compounds were verified by exact mass determination. Results are given for compounds **1a, b, i** and **j** below.

<u>General procedure for the preparation of **1a-i**:</u>

A mixture of **2a-i** 1 eqv., triethylorthoformate 2 eqv. and a catalytic amount of p-toluenesulfonic acid in tetrahydrofurane (10 ml) was heated to reflux for 30 min. The cooled mixture was evaporated in vacuo, then dissolved in ethyl acetate and washed with sat. $NaHCO_3$ aq.. The organic phase was dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column-chromatography on silica gel using CH_2Cl_2 / MeOH / NH_3aq. (9:1:1%) as an eluent.

The product was precipitated from THF as the hydrochloride by addition of a 1M etheral hydrogen chloride to the solution.

The following compounds were prepared in analogy with the above procedure:

2-Methoxyethyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1a**). Calc: $C_{25}H_{33}N_4O_4$ (M+H$^+$) = 453.2502. Found: $C_{25}H_{33}N_4O_4$ (M+H$^+$) = 453.2499.

2-Hydroxyethyl 1-(3-(4-ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1b**). Calc: $C_{24}H_{31}N_4O_4$ (M+H$^+$) = 439.2345. Found: $C_{24}H_{31}N_4O_4$ (M+H$^+$) = 439.2348.

n-Butyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1c**).

iso-Butyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1d**).

2-Methoxyethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1e**).

2-Hydroxyethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1f**).

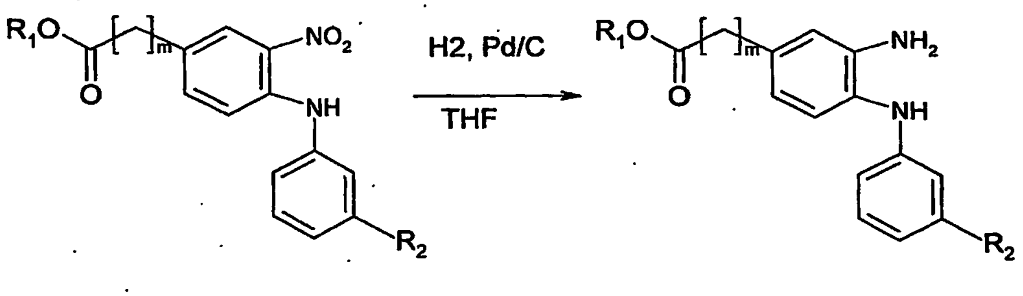
n-Butyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1g**).

iso-Butyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1h**).

5-(methoxycarbonylmethyl) 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole (**1i**). Calc: $C_{23}H_{29}N_4O_3$ (M+H$^+$) = 409.2240. Found: $C_{23}H_{29}N_4O_3$ (M+H$^+$) = 409.2222.

5-(2-hydroxyethoxycarbonylmethyl) 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole (**1j**): This compound was prepared from **1i** by transesterification. 0.2 g of **1i** was dissolved in 5 ml ethyleneglycol and heated to 100°C overnight. The resulting cooled mixture was taken up in EtOAc and washed with H_2O. The organic phase was dried $MgSO_4$ and evaporated in vacuo. The compound was purified by column chromathography using CH_2Cl_2/MeOH/NH_3aq. (9:1:1%) as an eluent. The

product was dissolved in THF and an ethereal solution of hydrochloric acid was added. The resulting hydrochloride of **1j** was filtered of. Yield: 85%. Calc: $C_{24}H_{31}N_4O_4$ (M+H$^+$) = 439.2345. Found: $C_{24}H_{31}N_4O_4$ (M+H$^+$) = 439.2363.



3a-i **2a-i**

The diamines of Table 2 were all prepared quantitatively by hydrogenation of the corresponding nitroanilines (**3**), according to the above scheme.

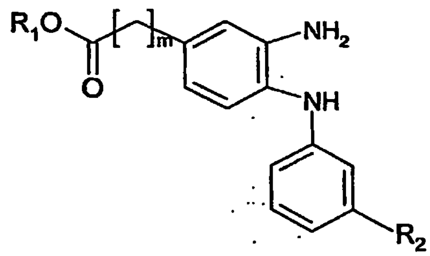
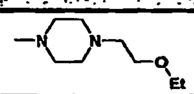
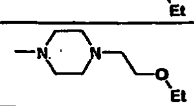
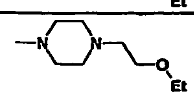
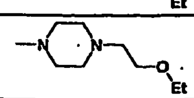
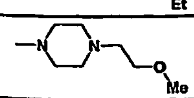
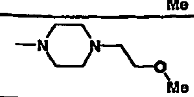
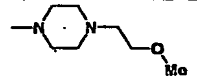
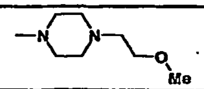
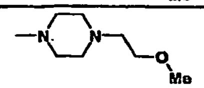


Table 2

Comp. No.	R1	R2	m	Starting material
2a	MeO(CH2)2		0	**3a**
2b	HO(CH2)2		0	**3b**
2c	Me(CH2)3		0	**3c**
2d	(CH3)2CHCH2		0	**3d**
2e	MeO(CH2)2		0	**3e**
2f	HO(CH2)2		0	**3f**

Comp. No.	R_1	R_2	m	Starting material
2g	$Me(CH_2)_3$		0	**3g**
2h	$(CH_3)_2CHCH_2$		0	**3h**
2i	Me		1	**3i**

General procedure for the hydrogenation of **3a-i**:

3a-i was suspended in tetrahydrofurane. Palladium catalyst (50 mg, 5% on activated carbon) was added and the mixture was hydrogenated at ambient pressure until the hydrogen uptake had ceased. The mixture was filtered through celite and the filtrate was evaporated to dryness to leave **2a-i**, quantitatively.

The following compounds were prepared in according to the above mentioned procedure.

2-Methoxyethyl 3-amino-4-(3-((1-ethoxyethyl-4-piperazinyl)-phenylamino)-benzoate **(2a)**.

2-Hydroxyethyl 3-amino-4-(3-(1-(ethoxyethyl-4-piperazinyl)-phenylamino)-benzoate **(2b)**.

n-Butyl 3-amino-4-(3-((1-ethoxyethyl-4-piperazinyl)-phenylamino)-benzoate **(2c)**.

iso-Butyl 3-amino-4-(3-((1-ethoxyethyl-4-piperazinyl)-phenylamino)-benzoate **(2d)**.

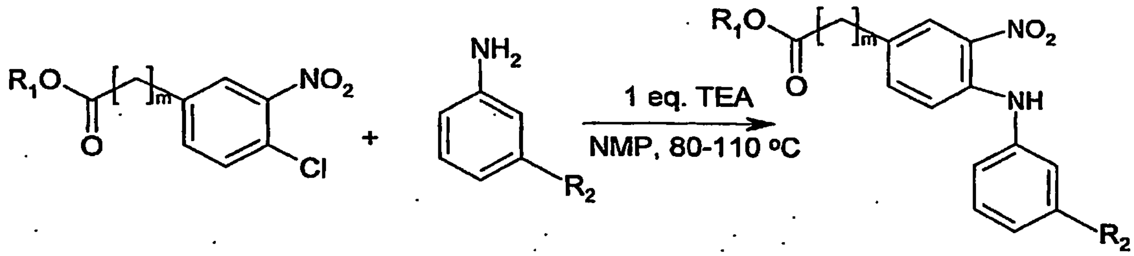
2-Methoxyethyl 3-amino-4-(3-((1-methoxyethyl-4-piperazinyl)-phenylamino)-benzoate **(2e)**.

2-Hydroxyethyl 3-amino-4-(3-(1-(methoxyethyl)-4-piperazinyl)-phenylamino)-benzoate **(2f)**.

n-Butyl 3-amino-4-(3-((1-methoxyethyl-4-piperazinyl)-phenylamino)-benzoate **(2g)**.

iso-Butyl 3-amino-4-(3-((1-methoxyethyl-4-piperazinyl)-phenylamino)-benzoate **(2h)**.

<u>5-Methoxycarbonylmethyl 2-(3-((1-methoxyethyl-4-piperazinyl)-phenylamino)-aniline</u> **(2i)**.



5a-e **4a-b** **3a-i**

The nitroanilines of Table 3 were prepared by reaction of 4-chloro-3-nitrobenzoates **5** with substituted anilines **(4)**, according to the above scheme.

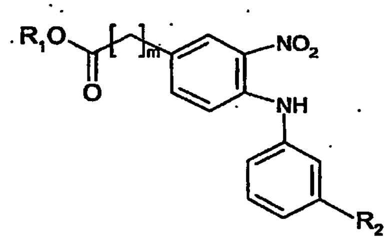
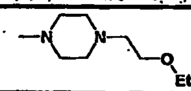
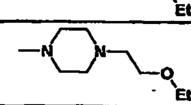
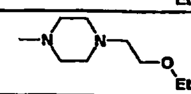
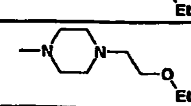
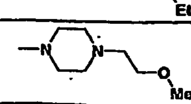
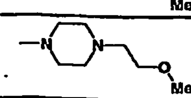
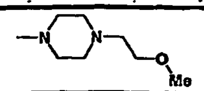
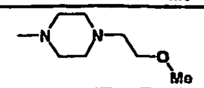
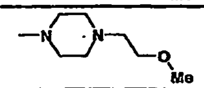


Table 3

Comp. No.	R_1	R_2	m	Starting material
3a	MeO(CH2)2		0	**4a, 5a**
3b	HO(CH2)2		0	**4a, 5b**
3c	Me(CH2)3		0	**4a, 5c**
3d	(CH3)2CHCH2		0	**4a, 5d**
3e	MeO(CH2)2		0	**4b, 5a**
3f	HO(CH2)2		0	**4b, 5b**

Comp. No.	R_1	R_2	m	Starting material
3g	$Me(CH_2)_3$		0	4b, 5c
3h	$(CH_3)_2CHCH_2$		0	4b, 5d
3i	Me		1	4b, 5e

General procedure for the preparation of compounds **3a-i**:

A mixture of **5a-e** 1 eqv., **4a-b** 1 eqv. and triethylamine 1 eqv. in NMP (10 ml) was heated to 110°C overnight. The cooled mixture was partitioned between water and ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column-chromatography on silica gel using a mixture of ethyl acetate and petroleum ether (1:1 v/v) as the eluent.

The following compounds were prepared in analogy with the above-mentioned procedure.

2-Methoxyethyl 3-nitro-4-(3-(1-(ethoxyethyl-4-piperazinyl)-phenylamino)-benzoate (**3a**).

2-Hydroxyethyl 3-nitro-4-(3-(1-(ethoxyethyl-4-piperazinyl)-phenylamino)-benzoate (**2b**).

n-Butyl 3-nitro-4-(3-((1-ethoxyethyl-4-piperazinyl)-phenylamino)-benzoate (**2c**)

iso-Butyl 3-nitro-4-(3-((1-ethoxyethyl-4-piperazinyl)-phenylamino)-benzoate (**2d**)

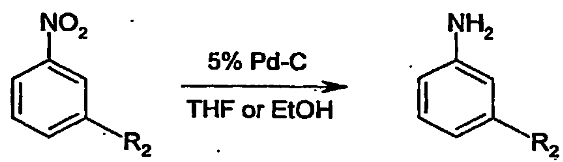
2-Methoxyethyl 3-nitro-4-(3-((1-methoxyethyl-4-piperazinyl)-phenylamino)-benzoate (**2e**).

2-Hydroxyethyl 3-nitro-4-(3-(1-(methoxyethyl)-4-piperazinyl)-phenylamino)-benzoate (**2f**).

n-Butyl 3-nitro-4-(3-((1-methoxyethyl-4-piperazinyl)-phenylamino)-benzoate (**2g**).

<u>*iso*-Butyl 3-nitro-4-(3-((1-methoxyethyl-4-piperazinyl)-phenylamino)-benzoate</u> **(2h)**.

<u>5-Methoxycarbonylmethyl 2-(3-((1-methoxyethyl-4-piperazinyl)-phenylamino)-nitrobenzene</u> **(2i)**.



6a-b **4a-b**

The substituted anilines of Table 4 were prepared by hydrogenation of the corresponding nitro compounds **6a-b** as exemplified by compound **4a** below.

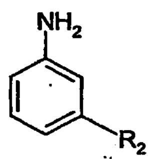
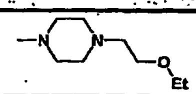
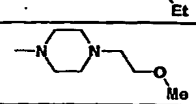


Table 4

Comp. No.	R_2	Starting material
4a		6a
4b		6b

<u>General procedure for the hydrogenation of compounds **6a-b**:</u>

To a solution of **6a** or **6b** in abs. ethanol (50 ml) was added palladium catalyst (100 mg, 5% Pd on activated carbon) and the mixture was hydrogenated at ambient pressure until the hydrogen uptake had ceased. Filtration through celite and evaporation of solvent left **4a** or **4b**, quantitatively.

The following compounds were prepared according to the above mentioned procedure:

1-Ethoxyethyl-4-(3-aminophenyl)-piperazine (**4a**).

1-Methoxyethyl-4-(3-aminophenyl)-piperazine (**4b**).

The 3-nitro-4-chlorobenzoicacid esters **5a-d** were prepared by esterification of the corresponding benzoic acids by the method mentioned below.

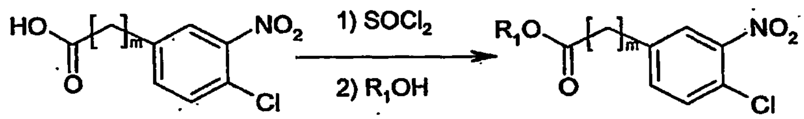


Table 5

Comp. No.	R_1	m	Yield %	X	Starting material
5a	$MeO(CH_2)_2$	0	62	Cl	4-chloro-3-nitrobenzoic acid
5b	$HO(CH_2)_2$	0	88	Cl	4-chloro-3-nitrobenzoic acid
5c	$Me(CH_2)_3$	0	96	Cl	4-chloro-3-nitrobenzoic acid
5d	$(CH_3)_2CHCH_2$	0	95	Cl	4-chloro-3-nitrobenzoic acid
5e	Me	1	55	F	4-fluorophenylacetic acid

General procedure for the preparation of **5a-d**:

A mixture of acid (10g) and thionylchloride (50 ml) was heated to reflux overnight. The excess of thionylchloride was removed by evaporation and alcohol (50 ml) was added. The resulting mixture was stirred at 80°C for 4 hours. The cooled solution was diluted with water (500 ml) and extracted with ethyl acetate (2 × 100 ml). The organic extract was washed with $NaHCO_3$ sat. and dried over magnesium sulphate and concentrated under reduced pressure. This gave the corresponding esters of a relatively high purity.

The following compounds were prepared according to the above mentioned procedure:

<u>2-Metyhoxyethyl 4-chloro-3-nitrobenzoate</u> **(5a)**.

<u>2-Hydroxythyl 4-chloro-3-nitrobenzoate</u> **(5b)**.

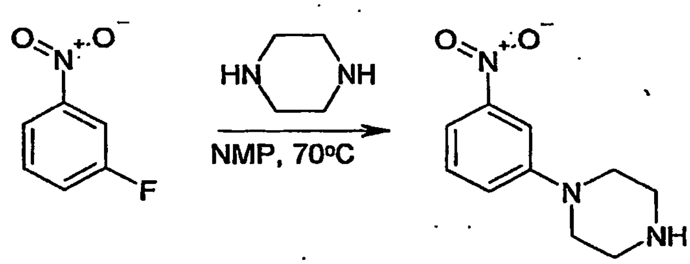
<u>*n*-Butyl 4-chloro-3-nitrobenzoate</u> **(5c)**.

<u>*iso*-Butyl 4-chloro-3-nitrobenzoate</u> **(5d)**.

<u>Methoxycarbonylmethyl-4-chloro-3-nitrobenzene</u> **(5e)**

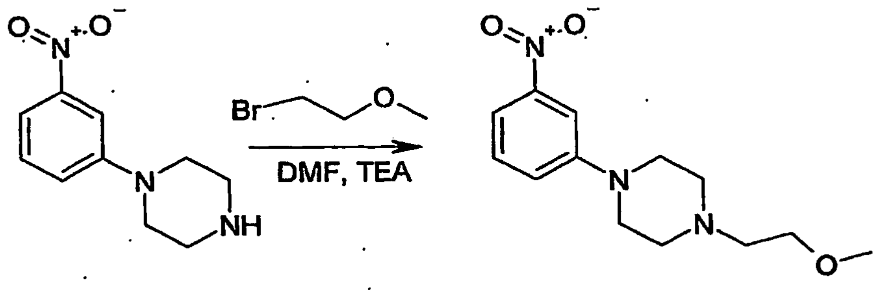
4-fluorophenylacetic acid (6g, 38.9 mmol) was suspended in 50 ml H_2SO_4 conc. And cooled to 0°C. To this suspension was added dropwise 1.75 ml HNO_3 during 30 min. and then the reaction mixture was striired at 0°C for another 3h. The yellow mixture was poured into is-water and the corresponding white crystals 4-fluoro-3-nitrophenylacetic acid 4.55g, 59% was collected and dried.

4-fluoro-3-nitrophenylacetic acid (4.55g, 22.9 mmol) was suspended in 50 ml MeOH and added 0.15 ml H_2SO_4 followed by reflux for 2h. After cooling the reaction mixture was poured into water and then added $NaHCO_3$ until pH>7. The extraction with EtOAc, drying with MgSO4 and evaporation in vacuo gave **5e**. Yield 4.25g, 87%.



<u>1-(3-Nitrophenyl)-piperazine</u>

A suspension of 3-fluoronitrobenzene (23 ml; 0.21 mol) and piperazine (55.5 g; 0.64 mol) in anhydrous NMP (30 ml) was heated to 70°C for five days. The cooled mixture was diluted with water (250 ml) and extracted with dichloromethane. The combined extracts were dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column-chromatography on silica gel eluting subsequently with mixtures of ethyl acetate and methanol (4:1 v/v) and (1:1 v/v) to leave the desired product as oily crystals (30.7 g; 71%).



6a-b

Ethoxyethyl 2-(4-(3-nitrophenyl)-1-piperazine (**6a**)

To a suspension of 1-(3-nitrophenyl)piperazine (8.18 g; 33.7 mmol) in DMF (80 ml) was added triethylamine (9.9 ml; 70.7 mmol) and the reaction was allowed to stir at RT forr 30 min. Then bromoethylethyl ether (6 ml; 50 mmol) was added, the mixture was stirred at ambient temperature for 2h. the reaction was worked up by evaporating DMF followed by resuspension in EtOAc and washing with $NaHCO_3$ sat. The organic phase was dried and evaporated to give an yellowish oil. This was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (8:2) as an eluent. Yield of **6a** (7.5 g; 81%).

The following compounds were prepared in analogy with Compound **6a**:

Methoxyethyl 2-(4-(3-nitrophenyl)-1-piperazine (**6b**) Yield 78%.

Example 2

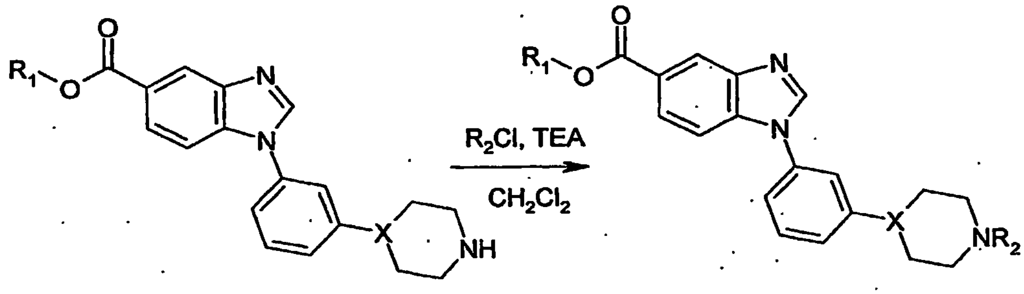
Method B

The following compounds were synthesised according to the method mentioned below.

Compound **7a** was synthesied from 2-Methoxyethyl 1-(3-(4-methoxycarbonyl-methyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate by dealkylation of the piperazine ring using the method by Kondo *et al*, J. Med. Chem., **1989**, 32 (3), 679-682. 2-Methoxyethyl 1-(3-(4-methoxycarbonylmethyl-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate was synthesised according to International Patent Publication No. WO 00/78728, example 1b.

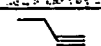
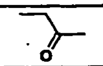
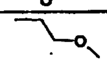
In the same way compound 7b was synthesised by dealkylation of 2-methoxyethyl 1-(3-(1-methoxycarbonylmethyl-4-piperidinyl)-phenyl)-benzimidazole-5-carboxylate using the same literature method as mentioned for **7a**. 2-methoxyethyl 1-(3-(1-methoxycarbonylmethyl-4-piperidinyl)-phenyl)-benzimidazole-5-carboxylate was

synthesised according to International Patent Publication No. WO 02/050057, Example 1d.



7a,b 8a-d

Table 6

Compound nr.	R_1	R_2	X	Yield	Starting material	Salt
8a	$MeO(CH_2)_2$		N	78	7a	formiate
8b	$MeO(CH_2)_2$		N	56	7a	formiate
8c	$MeO(CH_2)_2$		N	50	7a	formiate
8d	$MeO(CH_2)_2$		C	43	7b	formiate
8e	$HO(CH_2)_2$		N	93	8a	HCl

General procedure for the preparation of compounds **8a-d**:

To a solution of **7a** or **7b** in CH_2Cl_2 was added triethylamine 2 eqv. Followed by 2 eq. of R_2Cl. And stirring was maintained overnight at ambient temperature. The organic phase was washed with water, dried (MgSO4) and concentrated *in vacuo*. The crude products were purified by preparative LCMS using a gradient 20% B to 95% B in 13 min. A) 5mM $(NH_4)HCO_3/H_2O$ B) Acetonitrile. The collected fractions were pooled and acidified with formic acid before evaporation of the solvent. This gave **8a-c** as white solids.

The following compounds were prepared by the above mentioned method:

2-Methoxyethyl 1-(3-(4-(propargyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**8a**). Calc: $C_{24}H_{27}N_4O_3$ $(M+H^+)$ = 419.2083. Found: $C_{24}H_{27}N_4O_3$ $(M+H^+)$ = 419.2080.

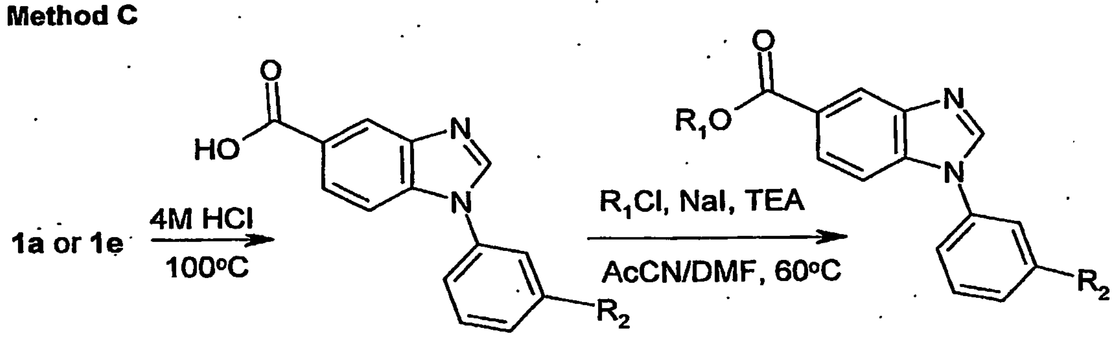
2-Methoxyethyl 1-(3-(4-(allyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**8b**).
Calc: $C_{24}H_{29}N_4O_3$ ($M+H^+$) = 421.2240. Found: $C_{24}H_{29}N_4O_3$ ($M+H^+$) = 421.2260.

2-Methoxyethyl 1-(3-(4-(2-oxo-propyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**8c**). Calc: $C_{24}H_{29}N_4O_4$ ($M+H^+$) = 437.2189. Found: $C_{24}H_{29}N_4O_4$ ($M+H^+$) = 437.2168.

2-Methoxyethyl 1-(3-(1-methoxyethyl-4-piperidinyl)-phenyl)-benzimidazole-5-carboxylate (**8d**). Calc: $C_{25}H_{32}N_3O_4$ ($M+H^+$) = 438.2393. Found: $C_{25}H_{32}N_3O_4$ ($M+H^+$) = 438.2382.

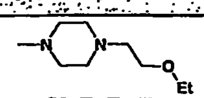
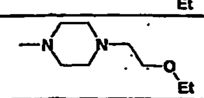
2-Hydroxyethyl 1-(3-(4-(propargyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**8e**). This compound was prepared from **8a** by transesterification using the same method as mentioned earlier for compound **1j**. Calc: $C_{23}H_{25}N_4O_3$ ($M+H^+$) = 405.1927. Found: $C_{23}H_{25}N_4O_3$ ($M+H^+$) = 405.1927.

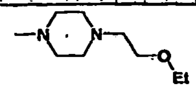
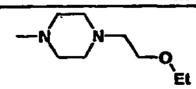
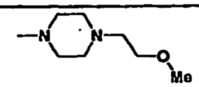
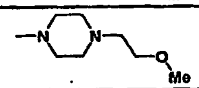
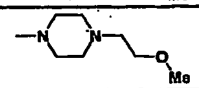
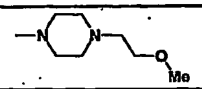
Example 3
Method C



9a,b **10a-h**

Table 7

Compound No.	R_1	R_2	Yield %	Starting material	Salt
10a	$PhCH_2$		42	**9a**	HCl
10b	$MeNHCOCH_2$		25	**9a**	HCl

Compound No.	R_1	R_2	Yield %	Starting material	Salt
10c	$EtNHCOCH_2$		50	**9a**	HCl
10d	$Me_2N(CH_2)_2$		80	**9a**	HCl
10e	$PhCH_2$		53	**9b**	-
10f	$MeNHCOCH_2$		48	**9b**	HCl
10g	$EtNHCOCH_2$		62	**9b**	HCl
10h	$Me_2N(CH_2)_2$		76	**9b**	HCl

General procedure for the preparation of compounds **9a** and **9b**:

Compound **1a** or **1e** was hydrolysed by dissolving the compound in 4M HCl and refluxed overnight. The reaction mixture was then cooled and evaporated in vacuo to give the crude acids **9a** and **9b**, respectively. No further purification was attempted at this point but the crude reaction mixture was used directly in the next step.

General procedure for the preparation of compounds **10a-h**:

The crude acid **9a** or **9b** was dissolved in acetonitrile / DMF 4:1 and then added triethylamine in excess (>3eq) and a small catalytic amound of NaI. The reaction mixture was stirred for 15 min after which the R_1Cl (2-3 eq.) was added and the reaction was then heated to 60°C overnight. After cooling the acetonitrile was evaporated and the resulting mixture was taken up in DCM and washed with water. The organic phase was dried $MgSO_4$ and evaporated give oily products. Column chromathography on silica gel using CH_2Cl_2/ MeOH/ NH_3aq. (9:1:1%) as an eluent gave the pure compounds **10a-h**.

The following compounds were prepared using the above method:

Benzyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10a**).
Calc: $C_{29}H_{33}N_4O_3$ $(M+H^+)$ = 485.2553. Found: $C_{25}H_{33}N_4O_3$ $(M+H^+)$ = 485.2549.

Methylcarbamoylmethyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10b**). Calc: $C_{25}H_{35}N_5O_4$ ($M+H^+$) = 466.2454. Found: $C_{25}H_{35}N_5O_4$ ($M+H^+$) = 466.2445.

Ethylcarbamoylmethyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10c**). Mp. 153-154°C.

2-Dimethylaminoethyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10d**). Calc: $C_{26}H_{36}N_5O_3$ ($M+H^+$) = 466.2818. Found: $C_{26}H_{36}N_5O_3$ ($M+H^+$) = 466.2811.

Benzyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10e**). Mp. 63°C.

Methylcarbamoylmethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10f**). Calc: $C_{24}H_{30}N_5O_4$ ($M+H^+$) = 452.2298. Found: $C_{24}H_{30}N_5O_4$ ($M+H^+$) = 452.2286.

Ethylcarbamoylmethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10g**). Calc: $C_{25}H_{32}N_5O_4$ ($M+H^+$) = 466.2454. Found: $C_{25}H_{32}N_5O_4$ ($M+H^+$) = 466.2459.

2-Dimethylaminoethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10h**). Calc: $C_{25}H_{34}N_5O_3$ ($M+H^+$) = 452.2552. Found: $C_{25}H_{34}N_5O_3$ ($M+H^+$) = 452.2646.

TEST METHODS

Test method 1

***In vitro* and *in vivo* Binding Activity**

The GABA recognition site and the benzodiazepine modulatory unit can selectively be labelled with ^{3}H-muscimol and ^{3}H-flunitrazepam, respectively.

1A: *In vitro* inhibition of ^{3}H-flunitrazepam (^{3}H-FNM) binding

Tissue Preparation

Preparations are performed at 0-4°C unless otherwise indicated. Cerebral cortex from male Wistar rats (150-200 g) is homogenised for 5-10 sec in 20 ml Tris-HCl (30 mM, pH 7.4) using an Ultra-Turrax homogeniser. The suspension is centrifuged at 27,000

x g for 15 min and the pellet is washed three times with buffer (centrifuged at 27,000 x g for 10 min). The washed pellet is homogenized in 20 ml of buffer and incubated on a water bath (37°C) for 30 min to remove endogenous GABA and then centrifuged for 10 min at 27,000 x g. The pellet is then homogenized in buffer and centrifuged for 10 min at 27,000 x g. The final pellet is resuspended in 30 ml buffer and the preparation is frozen and stored at -20°C.

Assay

The membrane preparation is thawed and centrifuged at 2°C for 10 min at 27,000 x g. The pellet is washed twice with 20 ml 50 mM Tris-citrate, pH 7.1 using an Ultra-Turrax homogeniser and centrifuged for 10 min at 27,000 x g. The final pellet is resuspended in 50 mM Tris-citrate, pH 7.1 (500 ml buffer per g of original tissue), and then used for binding assays. Aliquots of 0.5 ml tissue are added to 25 µl of test solution and 25 µl of ^{3}H-FNM (1 nM, final concentration), mixed and incubated for 40 min at 2°C. Non-specific binding is determined using Clonazepam (1 µM, final concentration). After incubation the samples are added 5 ml of ice-cold buffer and poured directly onto Whatman GF/C glass fibre filters under suction and immediately washed with 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

Results

25-75% inhibition of specific binding must be obtained, before calculation of an IC_{50}. The test value will be given as IC_{50} (the concentration (µM) of the test substance which inhibits the specific binding of ^{3}H-FNM by 50%).

$$IC_{50} = (\text{applied test substance concentration, } \mu M) \times \frac{1}{\left(\frac{C_o}{C_x} - 1\right)}$$

where
C_o is specific binding in control assays, and
C_x is the specific binding in the test assay.
(The calculations assume normal mass-action kinetics).

1B: *In vivo* inhibition of ^{3}H-FNM binding

Introduction

In vitro binding studies have demonstrated that the benzodiazepine [^{3}H]FNM binds selectively and with high-affinity to the $GABA_A$ receptor-ion channel complex. [^{3}H]FNM

can also be used for *in vivo* receptor labelling studies in mouse. Accumulation of [^{3}H]FNM binding will occur all over the brain as $GABA_A$ receptors are widely distributed. The specific binding of [^{3}H]FNM can be partly or completely prevented by simultaneous or prior administration of pharmacologically active benzodiazepines or by some benzodiazepine-like compounds.

Method

All test substances used are solutions prepared in 10% TWEEN 80. Groups of three female NMRI mice (25 g) are injected i.v. via the tail vein with 5.0 µCi of [^{3}H]FNM in 0.2 ml saline. Fifteen min after injection with [^{3}H]FNM the test substance is administered i.v. Twenty min after injection with [^{3}H]FNM, mice are killed by decapitation, the forebrains rapidly excised and homogenized in 12 ml of ice-cold 50 mM Tris-citrate, pH 7.1 using an Ultra-Turrax homogenizer. Three aliquots of 1 ml are immediately filtered through GF/C glass fibre filters and washed with 2 × 5 ml of ice-cold buffer. The amounts of radioactivity on the filters and in 200 µl of the homogenate are determined by conventional scintillation counting. Groups of untreated mice serves as controls. To determine non-specific binding groups of mice are injected with Clonazepam (25 mg/kg) i.p. 10 min before [^{3}H]FNM injection. Specific binding is the amount of binding in controls minus the amount of binding in Clonazepam treated mice.

Results

The ED_{50} value is determined from dose response curves. If only one dose of test substance is administered, the ED_{50} value is calculated as follows, provided that the inhibition of specific binding is within the range of 25-75%.

$$ED_{50} = (\text{administered dose, mg/kg}) \times \frac{1}{\left(\frac{C_o}{C_x} - 1\right)}$$

where C_o is specific binding in controls and C_x is the specific binding in mice treated with test substance.

Test method 2

PTZ Clonic Convulsions

The purpose of this test is to show antagonism of clonic convulsions induced by pentylenetetrazol (PTZ). PTZ induces clonic convulsions in mice after i.v. infusion. Antagonism of PTZ-induced convulsions is a measure for the agonistic character of ligands for the benzodiazepine recognition site.

Procedure

Female NMRI mice (Bomholdtgaard, Ry), 20 g, 6 mice in each group are administered i.v. with vehicle or test substance. After five minutes the PTZ-solution is infused intravenously at a speed of 0.7 ml/minute through a cannula placed in the tail vein. The time from initiation of the infusion to appearance of clonic convulsions is recorded.

The dose of PTZ required for inducing convulsion in each mouse is calculated as PTZ/kg body weight. Means ±sd for each experimental group of 6 mice is calculated. ED_{100} is calculated by linear regression expressing the dose increasing the PTZ threshold to 100 mg PTZ/kg.

The threshold of vehicle treated controls is in the range of 37-39 mg PTZ/kg. As a control in each series of experiments PTZ is infused into 6 vehicle treated mice.

Test method 3

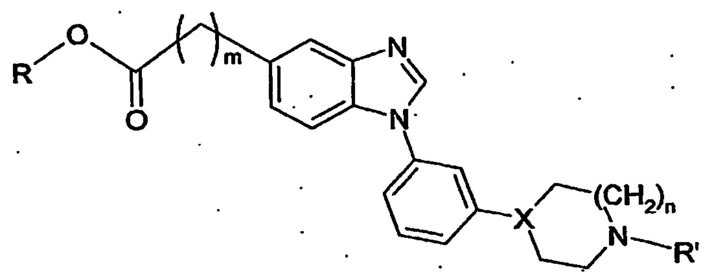
Evaluation of Efficacy

Selected compounds exhibiting a promising profile in the above tests may be evaluated with respect to efficacy and duration of action and compared to prior art as follows.

Aqueous solutions of the test substances (50 mg/ml isotonic glucose) are administered to pigs (25-30 kg) as bolus injections. The pigs are observed with respect to the time of induction of anaesthesia, the duration of anaesthesia and the normalising time following awakening from anaesthesia.

Claims

1. A compound of general formula I:



(I)

or an N-oxide thereof, or a pharmaceutically acceptable salt thereof, wherein R represents alkyl, hydroxyalkyl, alkoxyalkyl, R^aR^bN-alkyl, R^aR^bN-CO-alkyl, or phenyl-alkyl;

wherein R^a and R^b independently of each other represents hydrogen or alkyl;

R' represents alkoxyalkyl, alkoxyalkenyl, alkoxyalkynyl, alkylcarbonylalkyl, alkenyl, or alkynyl;

m is 0 or 1;

n is 1 or 2;

X represents N or CH.

2. The compound of claim 1, wherein n is 1 and X represents N.

3. The compound of claim 1, wherein n is 1 and X represents CH.

4. The compound of any one of claims 1-3, wherein R represents alkyl, hydroxyalkyl, or alkoxyalkyl.

5. The compound of any one of claims 1-3, wherein R represents R^aR^bN-alkyl, R^aR^bN-CO-alkyl, or phenyl-alkyl;

wherein R^a and R^b independently of each other represents hydrogen, methyl or ethyl.

6. The compound of any one of claims 1-5, wherein R' represents alkoxyalkyl.

7. The compound of any one of claims 1-5, wherein R' represents alkylcarbonylalkyl, alkenyl, or alkynyl.

8. The compound of claim 1, which is
2-Methoxyethyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1a**);
2-Hydroxyethyl 1-(3-(4-ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1b**);
n-Butyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1c**);
iso-Butyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1d**);
2-Methoxyethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1e**);
2-Hydroxyethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1f**);
n-Butyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1g**);
iso-Butyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**1h**);
5-(methoxycarbonylmethyl) 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole (**1i**);
5-(2-hydroxyethoxycarbonylmethyl) 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole (**1j**);
2-Methoxyethyl 1-(3-(4-(propargyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**8a**);
2-Methoxyethyl 1-(3-(4-(allyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**8b**);
2-Methoxyethyl 1-(3-(4-(2-oxo-propyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**8c**);
2-Methoxyethyl 1-(3-(1-methoxyethyl-4-piperidinyl)-phenyl)-benzimidazole-5-carboxylate (**8d**);
2-Hydroxyethyl 1-(3-(4-(propargyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**8e**);
Benzyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10a**);
Methylcarbamoylmethyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10b**);

Ethylcarbamoylmethyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10c**);
2-Dimethylaminoethyl 1-(3-(4-(ethoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10d**);
Benzyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10e**);
Methylcarbamoylmethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10f**);
Ethylcarbamoylmethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10g**);
2-Dimethylaminoethyl 1-(3-(4-(methoxyethyl)-1-piperazinyl)-phenyl)-benzimidazole-5-carboxylate (**10h**);
or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition containing a therapeutically effective amount of a compound according to any one of claims 1-8, or an N-oxide thereof, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

10. The use of a compound according to any one of claims 1-8, or an N-oxide thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of the GABA receptor complex.

11. The use according to claim 10, wherein the medicament is for inducing anaesthesia, pre-anaesthesia, muscle relaxation, or sedation, or for treatment, prevention or alleviation of fewer cramps or status epilepticus.

12. A method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of the GABA receptor complex, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of claims 1-8, or an N-oxide thereof, or a pharmaceutically acceptable salt thereof.